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Review

Innate and adaptive immunity against *Streptococcus pneumoniae* infection with emphasis on complement system

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ABSTRACT

Streptococcus pneumoniae (*S. pneumoniae*) is a human pathogen that causes several important and life-threatening invasive diseases such as pneumonia and meningitis with high morbidity and mortality throughout the world. After transmission to the host, *S. pneumoniae* is first confronted by the host's innate immune system before adaptive immune system activation. In the bloodstream, *S. pneumoniae* is specifically confronted by the complement system, which is a critical part of innate immunity. Complement system participates in host defenses including direct killing of bacteria through the assembly of a membrane attack complex, facilitation of phagocytosis through bacterial opsonization, recruitment and activation of immune cells, vasodilatation and increasing vascular permeability. Unfortunately, *S. pneumoniae* has developed several strategies to overcome innate and adaptive immune defenses in the respiratory tract. Extending our knowledge of the host immune response to *S. pneumoniae* is paramount for our improvement of pneumococcal disease diagnosis and treatment of patients. In this review, we outline the immune response developed during *S. pneumoniae* infection and the strategies developed to overcome host response with a focus on the complement system against *S. pneumoniae*.

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KEYWORDS: *S. pneumoniae,* innate immunity, adaptive immunity, complement system.

ABBREVIATIONS

IL: interleukin, MBL: Mannose-Binding Lectin, NLRs: (NOD)-like receptors, PAMPs: pathogen-associated molecular patterns, Psp: pneumococcal surface protein, *S. pneumoniae: Streptococcus pneumoniae*, Th: T helper, TLRs: Toll-Like Receptors, TNF: Tumor Necrosis Factor, Tregs: regulatory T cells.

INTRODUCTION

The most common pathogens causing community-acquired bacterial meningitis are currently *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis,* and *Listeria monocytogenes*, accounting for 70%, 10%, and 5% of cases, respectively [1, 2]. *S. pneumoniae* and *Neisseria meningitidis* are mostly responsible for two-thirds of cases in Europe and the United States [3], and *S. pneumoniae* is a serious bacterial pathogen of humans, which causes the majority of cases of pneumonia and many cases of meningitis and septicemia [4]. To date, despite advances in medical care, mortality from pneumococcal meningitis ranges from 16 to 37%, and neurological sequelae, including hearing loss, focal neurological deficits, and cognitive impairment, are estimated to occur in 30 to 52% of surviving patients [3]. After transmission to the host, *S. pneumoniae* is confronted

by the host's innate (or natural) immune response, which is immediate and by the adaptive (or specific) immune response, which is late. An important component of innate immunity to *S. pneumoniae* is the complement system, which is activated by three enzyme cascades: the classical, the alternative, and the mannose-binding lectin (MBL) pathways [5, 6]. The system includes a large number of soluble proteins that are found in the circulation and in tissues [7]. The complement molecules play a key role in the innate immune system through facilitating the clearing of pathogens and damaged cells by immune cells, direct bacterial killing by the pore-forming membrane attack complex, and also promoting the inflammatory response through the production of anaphylatoxins [8]. In addition, the complement molecules play an important role in adaptive immunity against *S. pneumoniae* through B lymphocytes' activation [9]. But, *S. pneumoniae* has evolved a number of ways to subvert the mechanisms of innate immunity, and this is likely to contribute to its pathogenicity. For example, the capsular serotype, proteins essential for virulence, as well the genotype, may all influence the ability of pneumococcus to resist the complement system and therefore its potential to cause disease. Thus, invasive *S. pneumoniae* infection may take place when the host is colonized with a pneumococcal strain to which it has not yet established immunity and when the host's immune system is altered. Here we review the innate and adaptive immune response against *S. pneumoniae* with a focus on complement system and the strategies developed by *S. pneumoniae* to overcome host immune response.

1. Host innate immunity against *S. pneumoniae*

S. pneumoniae is a human pathogen that causes bacteremia, pneumonia and meningitis with high morbidity and mortality throughout the world. Young children under the age of five, the elderly and people with pre-existing health conditions are particularly susceptible to these infections due to their weakened immune system and the inability to clear the pathogens before they become pathogenic [10, 11]. *S. pneumoniae* is transferred between people mainly by coughing and sneezing. After transmission to the host, *S. pneumoniae* is first confronted by the host's innate immune system, which plays a pivotal role in host defense at the earliest stages of infection [12].

At the nasopharyngeal site, *S. pneumoniae* is targeted by physical, cellular and molecular barriers of the respiratory tract. The first line defense in the respiratory tract is epithelial cells. These cells line the respiratory tract and protect against pneumococcus. Some epithelial cells known as goblet cells secrete mucus necessary for maintaining moisture and trapping foreign particles and pathogens [13, 14]. Ciliated epithelial cells function simultaneously with the mucus to clear pathogens. In addition to this mucociliary clearance, epithelial cells can directly kill pneumococcus by secreting antimicrobial peptides such as defensins, lactoferrin or apolactoferrin, and lysozyme [13, 15]. Defensins are small peptides produced by neutrophil cells that are active against a wide range of bacteria, fungi, and enveloped viruses. Due to their net positive charge and hydrophobicity, defensins are thought to exert their antimicrobial effects by permeabilizing the bacterial cytoplasmic membrane [16]. Lactoferrin acts bacteriostatically by depleting iron necessary for bacterial metabolism. Unbound lactoferrin (apolactoferrin) also has direct bactericidal properties, independent of iron scavenging, toward various pathogens, including *S. pneumoniae* [10]. In addition to lactoferrin, lysozyme is an antimicrobial innate immune molecule degrading peptidoglycan of the bacterial cell wall. It is a muramidase, which cleaves peptidoglycan and amino acids of *S. pneumoniae* leading to cell lysis. Deficiency in lysozyme led to an increased susceptibility to middle ear infection with *S. pneumoniae* and resulted in severe middle ear inflammation [10, 17]. This innate immune response to *S. pneumoniae* lung infection is critical for pathogen clearance and, one of the hallmarks of pneumococcal pneumonia is a rapid and exuberant response by neutrophils and macrophages [18, 19].

Neutrophils are phagocytic cells found in larger concentrations compared to any other white blood cells; they are generally the first to travel to the infection site. These phagocyte cells break down the cell walls of pathogens by producing granules such as defensins (primary granules) and lysosomes (secondary granules), which are antimicrobial peptides that can target *S. pneumoniae* [20]. In

addition, the expression of the cytokine IL-17 has been shown to correlate with the clearance of pneumococcal colonization, and both IL-17 and neutrophils were found to be necessary for an accelerated clearance in mice [21]. It is important to notice that neutrophil response changes with age. Neutrophil activity improves and strengthens in young adults, while infants experience minimal protection by neutrophils in their early days of life due to poor bactericidal function, impaired phagocytotic activity, low response to inflammatory signals, and reduced chemotaxis [22, 23]. Elderly populations experience impaired chemotaxis, which may lead to the overproduction of proteases by neutrophils. This causes an increase in inflammation levels in older subjects [11].

Macrophages also are phagocytic cells that engulf and directly kill *S. pneumoniae* [24]. Phagocytic activity in alveolar macrophages is important during early responses to subclinical infections [25], and during moderate *S. pneumoniae* lung infection. These cells are derived from monocytes. The monocytes migrate into the lungs, differentiating into monocyte-derived alveolar macrophages [26]. Deficiencies of phagocytic cells, such as neutropenia [27] or macrophage phagocytic receptor defects, lead to diminished pneumococcal clearance and increased risk of invasive pneumococcal disease in both mouse models and humans [28, 29]. In addition to directly eliminating pathogens, the macrophages can recruit other immune cells such as neutrophils *via* secretion of key cytokines like tumor necrosis factor (TNF), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which regulate effector cell functions and pulmonary inflammation [30-33]. Macrophages can also remove dead neutrophils [34, 35] and other cells *via* phagocytosis and apoptosis. The activation of these cells against *S. pneumonia* is dependent on pattern recognition receptors (PRRs). For example, toll-like receptors (TLRs) 2 and 4 work together to activate macrophages in the presence of pneumococci [36].

PRRs are receptors that recognize pathogen-associated molecular patterns (PAMPs). This receptor can be found on host cell surfaces, located intracellularly, or in secreted forms present in the bloodstream and interstitial fluids [24, 37]. There are two main types of PRRs that participate in the host's immune response to pneumococcus: TLRs and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) [36, 38]. TLRs are mostly found on cell surfaces as membrane-bound molecules that recognize PAMPs leading to the recruitment of immune cells and production of cytokines [39]. The main TLRs involved in pneumococcal infections are TLR2, TLR4, and TLR9. TLR2 is necessary in pneumococcal infection because it recognizes bacterial cell wall constituents [24, 39, 40]. TLR4 was the first TLR to be characterized and is needed for recognition of pneumococcal pneumolysin [40, 41]. TLR9 is intracellular and senses bacterial DNA within endosomes. It binds to CpG motifs on the DNA, and when activated it allows the release of cytokines [38, 39]. In addition to cytokine production, the activation of these TLRs facilitates the secretion of co-stimulatory molecules [39], which are necessary for activating T cells in adaptive immunity. In pneumococcal infections, NLRs recognize muramyl-dipeptide, which is a fragment of bacterial peptidoglycan in the cytosol [24] that promotes the production of cytokines and the recruitment of macrophages and monocytes to the infection site [42]. The expression and function of TLRs and NLRs decrease with age. Overall TLR cell signaling impairment causes a reduction in the cytokines produced, leading to poor defense against *S. pneumonia*, while decreased expression of NLR leads to weakened response to *S. pneumoniae*'s PAMPs [43].

2. Complement activation in *S. pneumoniae* infection

Once in the bloodstream, *S. pneumoniae* are confronted by the complement system [3], which is a critical part of innate immunity and plays an important role in the recognition and clearance of pathogens such as *S. pneumoniae* [44]. It is comprised of a set of small proteins that enhance the ability of antibodies and phagocytic cells to clear microbes and damaged cells. Complement system participates in host defenses through a range of mechanisms including direct killing of bacteria, facilitation of phagocytosis through bacterial opsonization, recruitment and activation of immune cells, vasodilatation and increasing vascular permeability. The direct killing of bacteria occurs after assembly of the membrane attack

complex, which forms pores in the pathogen membrane, inducing cell lysis [45].

Complement can be activated on pathogen surfaces through three distinct pathways: the classical pathway activated by antibody binding to an antigen, the alternative pathways, which are continuously activated at low levels but are only amplified on foreign surfaces due the absence of inhibitors on host cells and the lectin pathway which is activated by MBL recognition of carbohydrates on microbial surfaces [46]. These pathways depend on different molecules for their initiation, but all the pathways converge at C3 (which is the most abundant complement protein found in the blood), resulting in the formation of the activation products C3a, C3b, C5a and the membrane attack complex (C5b-9) [47]. In order to identify which pathway plays the major role in response to pneumococcal infection, different investigations have been done on mice deficient in complement pathways. Brown *et al*., in 2002, stated that the classical pathway is the most important pathway in response to pneumococcal infection [48]. The importance of the classical pathway for immunity against pneumococci is further supported by the observation that deficiency in classical complement components such as C1q, C4 and C2 is associated with recurrent and severe pneumococcal infections [49, 50]. As observed for the classical pathway, studies that are more recent found an important contribution by the lectin pathway in *S. pneumonia* infection. Ali *et al*. (2012) showed that mice strains deficient in the lectin pathway, which can still activate complement *via* the classical pathway and the alternative pathway, are highly susceptible to pneumococcal infection [51]. A meta-analysis on human studies suggested that MBL deficiency might be associated with susceptibility to invasive pneumococcal disease [52]. Brouwer *et al*. (2013) confirmed this in a cohort study, showing that MBL deficiency was associated with a considerable increase in susceptibility to meningitis caused by *S. pneumoniae* [53]. Thus, the importance of the different complement pathways' role in pneumococcal infections needs to be further investigated.

However, irrespective of the specific pathway for complement activation, the complement system protects against infection in three ways. First, it generates large numbers of activated complement proteins that bind to pathogens, opsonizing them for engulfment by phagocytes bearing complement receptors [18]. Second, the small fragments of some complement proteins act as chemoattractants to recruit more phagocytes to the site of complement activation, and to activate these phagocytes [54]. Third, the terminal complement components damage certain bacteria by creating pores in the bacterial membrane [18]. In pneumococcal infection, complement-activated molecules contribute to pneumococcal infection clearance, anaphylaxis and inflammation resistance. A protein complex, convertase 3/5, transiently formed by C3b and C4b, and the protease fragment Bb and C2b, activates complement components C3 or C5 and promotes opsonization, amplification and/or generation of effectors molecules [54]. Upon activation of C3 and C5 by a protein complex convertase 3/5, the effector fragments C3a and C5a are released. These fragments, also called anaphylatoxins, exert numerous immunomodulatory, chemotactic and/or cell-activating functions [54]. Complement protein fragments C4a, C3a and C5a (with increasing order of activity) are all anaphylotoxins, which cause the degranulation of basophils and mast cells as well as contraction of smooth muscles [54]. In addition to its function as anaphylatoxins, C5a and the membrane attack complex are both chemotactic factors. C5a is also a potent activator of neutrophils, basophils and macrophages and allows the induction of adhesion molecules on vascular endothelial cells. C3b and C4b fragments can act as opsonins when deposited on the surface of microorganisms to facilitate their removal; this process is known as opsonization. Therefore, these fragments can bind to the complement type 1 receptor present on phagocytic cells and thus promote opsonic phagocytosis [8]. Other biologically active products from degradation of the C3 fragment (iC3b, C3d and C3e) can also bind to different cells through separate complement receptors and modulate the functions of these cells [8]. However, autoimmune reactions, age-related modifications, deficiencies, and genetic alterations in complement proteins often exacerbate complement-mediated damage and tip the balance from protection to destruction [55].

Recently, it is becoming increasingly evident that complement also plays an important role in adaptive immunity involving T and B cells that help in elimination of pathogens [56]. As a bridge to adaptive immunity, the complement molecule C3 leads to B cell activation through complement receptors CD21 and CD35 [9]. Complement molecules also assist in the clearance of immune complexes, cellular debris, and apoptotic cells and have been associated with early development and tissue repair. Thus, complement exerts much broader functions in immune surveillance and homeostasis [8]. Such a broad involvement in physiological processes can only be achieved through close communication of the complement system with other regulatory systems. Indeed, numerous relationships involving crosstalk between complement and other biological systems have been described, underscoring a role for complement as an immunological mediator, rather than merely an antimicrobial effector [57].

3. Complement system deficiency in *S. pneumoniae* infection

Primary immunodeficiency diseases are defects of the immune system that lead to increased susceptibility to infection and/or immune dysregulation [58]. Deficiencies of components of complement have been described [59]. They include early components of the classical (C1, C4, C2), and alternative (factor D, H, I, properdin) pathways, C3 deficiency, deficiencies of the membrane attack complex (C5-C9) and defects of lectin pathway (MBL and MBL-associated serine proteases). Deficiencies in the complement system are well known to increase the risk of bacterial infections [53] and patients with these deficiencies are susceptible to encapsulated bacterial infections such as *S. pneumoniae* [60]. Thus, several studies have quantified complement molecules in blood and cerebrospinal fluid, and have shown that complement levels are correlated with severity and disease outcome [61, 62]. When it is deregulated or over activated due to host genetic or microbial virulence factors, complement can turn from a homeostatic effector to a pathological effector that drives various inflammatory disorders and cancers, reflecting the multifaceted nature of complement interactions [63].

Forty percent of patients with C3 deficiency have an increased susceptibility to pneumococcus with invasive pneumococcal disease in most cases [64]. In patients with defects of the classical pathway, 15% with deficiencies in C2 have invasive pneumococcal disease [64]. *S. pneumoniae* was also isolated more sporadically from patients with other deficiencies of the classical pathway, such as C1q, C1r or C1s, and from patients with deficiency in alternative pathway components such as properdin, factor D and factor I [60]. The importance of the classical pathway for immunity against *S. pneumoniae* is further supported by the observation that deficiency in classical complement components such as C4 and C2 in addition of C1q is associated with recurrent and severe pneumococcal infections [49, 50]. Similarly, mouse models of complement deficiency reveal an increased susceptibility to pneumococcal sepsis [48]. Recurrent and invasive *S. pneumoniae* infections occur in individuals with defects in the terminal components of the complement pathway C5-C9 [65]. The absence of alternative pathway factors such as factor D and properdin may also result in a similar increase in risk of infections. Defects of MBL have been associated with recurrent respiratory tract infections such as pneumonia and meningitis [65]. Recently, a case of primary pneumococcal peritonitis has been described. This case has revealed a family with compound heterozygous deficiency for complement factor I that is a serine protease acting as a regulator of all complement pathways by cleaving and inactivating C4b and C3b, respectively [66, 67].

4. *S. pneumoniae* mechanisms to escape host innate immune defenses

S. pneumoniae has a large selection of virulence factors that promote adherence, invasion of host tissues, and allows it to escape host immune defenses. As the most important virulence factor, the capsule repulses the sialic acid residues of mucus by its negative charge, thereby decreasing the likelihood of entrapment [14, 68]. *S. pneumoniae* capsule helps to initiate infection by allowing adhesion to host cells and inflammation, while also providing protection from the host's immune system. Moreover, the capsule inhibits phagocytosis

by immune cells, prevents the recognition of the bacteria by host receptors and complement factors, and avoids neutrophil traps [42, 68, 69]. *S. pneumoniae* also expresses neuraminidase to target host cells. Neuraminidase is known for cleaving sialic acid from glycoproteins. This activity can lead to the removal of sialic acid from lactoferrin, which hinders lactoferrin's bactericidal effect [10]. Neuraminidase is capable of deglycosylating mucus glycoconjugates, thereby decreasing mucus viscosity and preventing mucus entrapment [3]. *S. pneumoniae* also produce autolysin, an enzyme involved in autolysis of bacteria which results in the release of pneumolysin and other components from within the cell [70, 71]. Pneumolysin, a pore-forming toxin, is a putative virulence factor. It binds to membranes containing cholesterol, and forms pores, which later lead to host cell lysis. Pneumolysin decreases epithelial cell ciliary beating, thereby enabling the pneumococcus to bind to epithelial cells without being removed with the mucus [72, 73]. Thus, autolysins promote colonization of nasopharyngeal cells due to the release of pneumolysin during cell wall degradation. In addition to causing cell lysis, pneumolysin plays a role in promoting the formation of biofilms [74]; it reduces mucus clearance of the bacterium, and it can interfere with the host's immune system [75].

In addition to the respiratory mucus as natural barrier, lysozyme is also an important natural barrier and the pneumococcus has developed several strategies to overcome the lysosyme system. Peptidoglycan, wall teichoic, and lipoteichoic acids are the main components of *S. pneumoniae*'s cell wall and acetylated peptidoglycan molecules of the pneumococcal cell wall are specifically prone to lysozyme destruction. These glycan chains can undergo secondary modifications such as deacetylation and O-acetylation by pneumococcus enzymes, peptidoglycan N-acetylglucosamine-deacetylase A and O-acetyltransferase, respectively. These modifications aid in *S. pneumoniae*'s virulence by making the cell resistant to lysozyme [10, 76].

Expression of pneumococcal surface protein A (PspA), a choline-binding protein expressed on the outer surface of the cell, prevents apolactoferrin-mediated killing. Pneumococcal phosphorylcholine may bind to the platelet-activating factor receptor on activated epithelial and endothelial cells leading to the mechanism of epithelial transmigration. By binding to the platelet-activating factor receptor, the pneumococcus may enter the platelet-activating factor receptor recycling pathway, which transports the bacterium to the basal membrane of the host epithelial cell, which may lead to invasive disease [77, 78]. Another mechanism involves the binding of the pneumococcal choline-binding protein C (PspC) to the extracellular portion of epithelial polymeric immunoglobulin receptor as an important factor for facilitating colonization and invasive disease [79].

Against complement system, *S. pneumoniae* have developed two ways to minimize complement-mediated opsonization and phagocytosis. First, pneumococci undergo a second phase variation and become encapsulated. The polysaccharide capsule serves as a nonspecific barrier, significantly reducing complement deposition on the bacterial surface and limiting subsequent interaction with phagocytes. Second, pneumococcal surface proteins PspA, PspC, and pneumolysin target specific complement components, thereby reducing complement-mediated bacterial clearance [80]. PspA inhibits C1q and subsequent C3b deposition. PspC blocks the formation of C3 convertase (C3bBb), leading to lower C3b production and limiting opsonophagocytosis [44]. Recent *in vitro* studies showed that PspA and PspC work synergistically to limit complement-mediated adherence and transfer to phagocytes [44]. Pneumolysine released during pneumococcal autolysis can also limit complement system function. The easy binding of pneumolysin to the Fc portion of IgG potentially activates the classical complement pathway away from the bacteria, leading to the depletion of complement factors and limiting opsonophagocytosis that helps to increase the virulence of bacteria [81, 82]. Thus, invasive *S. pneumoniae* infection may take place when the host is colonized with a pneumococcal strain to which it has not yet established immunity and when the host's immune system is altered.

5. *S. pneumonia*e interaction with adaptive immunity

Adaptive immune responses can be broken down into two types of responses: humoral and cell-

mediated. While humoral immunity involves B cells that produce antibodies specific to antigens, cell-mediated immunity involves T cells that can directly kill pathogenic cells [56]. All the cells involved in adaptive immune system respond to specific antigens from pathogens.

Regarding B cells in *S. pneumoniae* infection, after antigen stimulation by pneumococcal capsular polysaccharides, naïve B cells can differentiate into IgM^+ memory B cells and produce pneumococcal-specific antibodies through T cell-dependent or T cell-independent pathways [83]. Later, during hypermutation and class switching, some pneumococcal-specific IgM^+ B cells will differentiate to pneumococcal-specific IgG^+ or IgA^+ memory B cells or plasma cells. At birth, maternal IgG antibodies protect infants until 27 days of age, based on the half-life of IgG. Once maternal antibodies have been depleted, the infant's ability to protect itself *via* steady antibody generation experiences a delay until age two [84]. Following *S. pneumoniae* colonization, specific IgA antibody is observed in mucosal areas of the nose and saliva and is recognized as a key humoral defense against infection at the mucosal sites [83, 85]. Secretory IgA interferes with binding to the nasopharyngeal mucosa and is important for opsonizing *S. pneumoniae* and promoting phagocytosis by antigen-presenting cells and neutrophils [3, 10]. In an $IgA^{-/-}$ mouse model, infection was observed despite a high level of IgG antibodies while no *S. pneumoniae* was found in $IgA^{+/+}$-immunized mice. Therefore, IgA antibodies play a necessary role in the regulation of *S. pneumoniae* colonization in the nasal cavity [86]. These observations were reinforced by clinical studies in IgA-deficient patients who have reduced vaccine responses and have higher rates of recurrent infections and bronchiectasis [87], suggesting the pivotal role of IgA in the clearance of *S. pneumoniae*. Moreover, IgM is also important for immune responses against *S. pneumoniae* infection. The depletion of IgM abrogates the protective effect of antibodies in young adults, and lower level of IgM+ memory B cells has been implicated in the high incidence of lethal infections in the elderly population, suggesting that IgM is also critical for immune responses against infection [88-90]. The critical role of IgM in pneumococcal disease could be explained by the fact that IgM is the first antibody produced after neo-antigen stimulation, prior to IgA or IgG. Defects in IgM may affect antigen-specific IgA^+ or IgG^+ B cell maturation and function, thereby impairing late humoral responses and consequently leading to more severe bacterial infections. In addition, due to its pentameric structure, IgM would be expected to agglutinate and opsonize the pathogen more efficiently, and IgM is a key to the complement cascade activation in response to infection [83, 90].

Similarly to humoral immunity, cell-mediated immunity is also important for clearance of *S. pneumoniae*. $CD4^+$ T cells are activated *via* interaction with antigen-presenting cells and co-stimulatory molecules, resulting in differentiation into T helper 1 (Th1) and 2 (Th2) cells. Th1 cells stimulate a cellular-mediated immune response by producing cytokines such as interferon-gamma (IFN-γ) that activate and recruit other immune cells such as macrophages and natural killer cells while Th2 helper cells release IL-4 cytokines and aim to facilitate a humoral immune response by interacting with B cells and stimulating antibody production [91]. In addition to Th1 and Th2, recent studies suggest a crucial role of interleukin-17 secreting $CD4^+$ T cells (T helper type 17 or Th17) and regulatory T cells (Tregs) in mediating the clearance of pneumococcal colonization [21, 92, 93]. Th17 cells release cytokine IL-17 that is needed for recruiting and activating macrophages, monocytes, and neutrophils to sites of infection and promote the clearance of *S. pneumoniae*. Treg cells are necessary for regulating Th17's production of IL-17, and imbalance between Tregs and Th17 cells can lead to autoimmune disease [94]. Finally, cytotoxic T cells can directly kill infected cells. Similarly, natural killer T-cells are also important for clearance of pneumococci through a cytotoxicity mechanism [24, 70].

Despite the various mechanisms of the adaptive immune system, *S pneumoniae* have developed several methods to limit it destruction. First, the capsule itself prevents binding of IgA [44]. Second, capsule-bound IgA is cleaved by a pneumococcal IgA1 protease. This protease cleaves IgA at the hinge region, inhibiting IgA-mediated opsonization

and promoting binding to the respiratory mucosa [95]. The remaining Fab fragment of IgA binds to the cell wall, thereby exposing choline-binding proteins and decreasing the negative charge of the capsule, which also facilitates bacterial adhesion to the epithelial cell [3, 95]. In addition, adaptive immune response varies with age. The efficacy of the adaptive immune cells diminishes in elderly populations with reduced production of antibodies, immunoglobulin class switching, and cell maturation, which promotes *S. pneumoniae*'s colonization [11]. There is also an overall reduction in naïve T cells with age due to thymus involution [96]. Diminished responses from the adaptive immune cells explain the higher incidence rates of pneumococcal diseases in these high-risk age groups.

CONCLUSION

S. pneumoniae is transferred between people mainly by coughing and sneezing and is one of the most common causes of meningitis and pneumonia in both industrialized and developing countries. After transmission to the host, *S. pneumoniae* is first confronted by the host's innate immune system, which plays a pivotal role in host defense at the earliest stages of infection. At the nasopharyngeal site, *S. pneumoniae* is targeted by physical, cellular and molecular barriers of the respiratory tract, which utilize a variety of strategies to obstruct microbe entry. The complement system is one of the major mechanisms by which *S. pneumoniae* recognition is converted into an effective host defense against initial infection. Deficits in the complement system are associated with high prevalence of serious pneumococcal infections. Despite the recurrent epidemics of meningitis and also the exponential number of cases of *S. pneumoniae* infection in sub-Saharan Africa, more particularly in Burkina Faso, data on deficits of the complement system are very poor or even non-existent.

AUTHOR CONTRIBUTIONS

Study concept, design, definition of intellectual content and literature search: YEH and ARN. Manuscript preparation: YEH, ARN and DK. Manuscript review: YEH, ARN, DK, DK, OO, GO and YT.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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